and Pine Island Glacier in Antarctica, the two glaciers with the earliest recorded accelerations, are among the deepest outlets with grounding lines over 1000 m below sea level. It is likely that the large outlet glaciers such as these have eroded deeper basins than the smaller adjacent glaciers that have accelerated more recently.

In this context, a key characteristic of troughs eroded by tidewater glaciers is that they end with a shallower terminal moraine at the site of their maximum glacial cycle extent. In warmer climates, they retreat from this advanced position, leaving this moraine, or sill, as a barrier that prevents deeper water seaward of the sill from reaching the deep grounding line (see the figure). Once breached, however, the warm, salty water will sink in the cold, fresh water behind the sill and reach ice at the grounding line. Increased pressure at these greater depths lowers the melting point of this ice, increasing the melting efficiency of the warmer water. Rapid melting results. This process has been modeled for the observed sill geometry in front of and beneath Pine Island Glacier (18).

Surface meltwater cannot explain this common behavior. Penetration of surface meltwater to the glacial bed in Greenland can lead to seasonal flow acceleration (19), but the annually averaged increase in speed is only a few percent. In the case of Helheim Glacier, the relative intensities of warm summers were not associated with the observed changes in glacier speed (20). And surface melting is uncommon for any of the Antarctic glaciers cited here.

Outlet glacier acceleration will probably continue. As sea ice growth and decay diminish, warmer waters will reach shallower depths and access shallower tidewater glaciers, as well as move northward along Greenland's coasts. This will lead to increasing discharge of grounded ice and accelerating sea level rise. Increased discharge could encourage longer ice shelves, helping to protect the grounding lines, but this has not been observed because ice shelves have failed to grow in front of accelerating glaciers and retreat is exceeding historical bounds. Retreating glaciers lengthen the distance warmer water must travel from any sill to the grounding line, and eventually tidewater glaciers retreat to beds above sea level. This might limit the retreat in Greenland but will save neither West Antarctica, nor the equally large subglacial basin in East Antarctica where submarine beds extend to the center of the ice sheet.

References and Notes
21. I thank D. Holland for assistance in preparation of the manuscript.

The authors are in the Department of Molecular Genetics, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390–9046, USA. E-mail: mike.brown@utsouthwestern.edu, joe.goldstein@utsouthwestern.edu.

BIOMEDICINE

Lowering LDL—Not Only How Low, But How Long?

Michael S. Brown and Joseph L. Goldstein

The causal relation between plasma low-density lipoprotein (LDL) cholesterol (LDL-C) levels and coronary heart disease is well established. Compelling evidence from between-country comparisons shows that large and lifelong diet-related differences in LDL-C levels are associated with 10-fold differences in coronary mortality (1) (see the figure). Strong support comes from observations on genetic diseases such as heterozygous familial hypercholesterolemia, in which mutations in the LDL receptor gene double LDL-C levels throughout life and increase the risk of early heart attack by more than 10-fold (2). So, it has been somewhat disappointing that treatment with cholesterol-lowering statins for 5 years reduces the incidence of heart attacks by only 40%, even when LDL-C concentration is reduced by 80 mg/dl (3), a reduction that should give much more protection based on the population studies. A likely explanation is provided by Cohen, Hobbs, and their colleagues in this week’s issue of the New England Journal of Medicine (4). In lowering LDL levels, the appropriate consideration may be not only how low, but also how long.

Cohen et al. studied middle-aged Americans with lifelong low LDL levels, owing to loss-of-function mutations in the gene encoding PCSK9, a secreted enzyme of the serine protease family. In a small number of subjects with severe nonsense mutations, the concentration of LDL-C was reduced by 38 mg/dl, and the prevalence of coronary heart disease declined by a remarkable 88%. In a larger number of subjects with a less severe missense mutation, LDL-C concentration was reduced by only 21 mg/dl, yet coronary heart disease incidence declined by 47%.

What is the function of PCSK9, and how do mutations in the PCSK9 gene lower the concentration of LDL? Experiments in mice showed that overproduction of PCSK9 in liver and cultured hepatocytes severely reduces the number of LDL receptors (5, 6). The simplest hypothesis is that PCSK9 directly catalyzes the breakdown of LDL receptors, but this has not been demonstrated experimentally. Inasmuch as LDL receptors mediate high-efficiency removal of LDL from plasma, a reduction in the number of LDL receptors causes LDL to accumulate.

Ablation of the PCSK9 gene in mice through gene-knockout technology increased the number of LDL receptors in liver and enhanced the clearance of LDL from the plasma (7). This striking finding indicates that PCSK9 functions tonically in mice to keep LDL receptor number lower and plasma LDL concentration higher than they would be otherwise. PCSK9 appears to have the same effect on LDL in humans. A role for PCSK9 was first recog-
Atherosclerosis is a chronic disease that be
tained relatively low LDL levels
have now demonstrated the opposite effect—namely, that loss-of-
Individuals harboring either of these mutations had plasma LDL levels averaging 40% lower than those without them. These mutations were rare (0.1%) in Americans of European ancestry (Caucasians) (11).
Cohen et al. (4) now demonstrate the cardio-
ological clues to lower LDL levels in PCSK9. They analyzed data from a prospective study of 15,792 Caucasians and African-
Americans from four U.S. communities that was initiated in 1987 (12). These randomly selected individuals aged 53 years of age at entry, and have been followed for 15 years. Among the 3278 African-American individuals without a PCSK9 mutation, LDL-C levels averaged 138 mg/dl, and 319 of these individuals developed symptomatic coronary heart disease for an incidence of 9.7%. Among the 85 African-
American individuals with a PCSK9 nonsense mutation, LDL-C concentration was reduced by 38 mg/dl (to 100 mg/dl). Remarkably, only one of these 85 people (1.2%) developed coronary heart disease, an 88% reduction. In these protected individuals, coronary heart disease was rare despite a high prevalence of hypertension (37%) and diabetes (13%). Although the number of subjects is small, the extremely low inci-
dence of coronary heart disease in African-
Americans with PCSK9 nonsense mutations is consistent with other studies (see the figure) that show an extremely low incidence of coronary heart disease in populations with lifelong low cholesterol levels (1, 13). Among Caucasians in the same study, 301 individuals (3.2%) had a missense mutation that lowered LDL-C levels by only 21 mg/dl, yet reduced coronary heart disease incidence by 47%.

Why does lowering of LDL-C concentration by 40 mg/dl by a PCSK9 mutation reduce coronary heart disease incidence by 88%, whereas a 40-mg/dl lowering with a statin reduces coro-
Because of its LDL-elevating effect, athero-
ds not be certain that the atherogenic effect of PCSK9 is due solely to its LDL-elevating action. A PCSK9 inhibitor should synergize with cholesterol-depletion therapy in raising LDL receptor number and lowering plasma LDL concentration (7).

Admittedly, our knowledge of the patho-
genesis of atherosclerosis is incomplete, and more research is needed. We do not know precisely how LDL particles cause the inflamma-
tory and proliferative lesions of the atheroscle-
terotic plaque. Although we measure LDL by its

low incidence of side effects, primarily rare muscle necrosis and occasional increases in circulating liver enzymes (3).

The use of cholesterol-lowering drugs has been restricted to individuals suspected to be at high risk for myocardial infarction. Treatment is usually initiated at ages in which the atheroscle-
rotic process is likely to have already advanced. One objection to earlier use has been cost. This objection may be overcome by the availability of low-cost generic statins. Generic statins are an option for relatively young individuals with LDL-C levels that are “normal” for the U.S. pop-
ulation, but are above the levels that offer protec-
tion from heart attacks. Selection of individuals for preventive treatment would improve if we had reliable noninvasive methods to diagnose early atherosclerosis.

Current data justifying more aggres-
sive drug therapy at the first sign of hypertension or diabetes, even when blood pressure and glucose levels can be controlled. Current guidelines of the U.S. National Institutes of Health–spon-
sored Cholesterol Education Treatment Panel (19) recommend lowering plasma LDL-C concent-
tration to 70 mg/dl in people at high risk for early heart attack. Concern over whether these recommended levels are too low should be tem-
bered by the reality that the average level of plasma LDL-C in newborn infants throughout the world is only 50 to 70 mg/dl (20) and that LDL-C levels remain at or below 100 mg/dl on average throughout life in populations that con-
some low-fat diets (13).

Although studies of PCSK9 are still in their infancy, they suggest a new approach to enhanc-
ing the effectiveness of statins and other drugs that deplete cholesterol in the liver and raise LDL receptor number. Mouse experiments indicate that SREBP, the transcription factor that increases the expression of LDL receptors, also increases the production of PCSK9 (21, 22). Depletion of liver cholesterol activates SREBPs, thereby increasing LDL receptor numbers (17), but also increasing PCSK9 levels (23). The PCSK9 destroys some of the LDL receptors, thereby partially negating the LDL-lowering effect. A PCSK9 inhibitor should synergize with cholesterol-depletion therapy in raising LDL receptor number and lowering plasma LDL concentration (7).

Among the 85 African-
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-Americans with PCSK9 nonsense mutations is consistent with other studies (see the figure) that show an extremely low incidence of coronary heart disease in populations with lifelong low cholesterol levels (1, 13). Among Caucasians in the same study, 301 individuals (3.2%) had a missense mutation that lowered LDL-C levels by only 21 mg/dl, yet reduced coronary heart disease incidence by 47%.

Why does lowering of LDL-C concentration by 40 mg/dl by a PCSK9 mutation reduce coronary heart disease incidence by 88%, whereas a 40-mg/dl lowering with a statin reduces coronary heart disease prevalence by only 23% on average (3)? The most likely answer is duration. People with nonsense mutations in PCSK9 likely have maintained relatively low LDL levels throughout their lives. People in statin trials have had their LDL levels lowered for only 5 years. Atherosclerosis is a chronic disease that begins in the teenage years (14). In a statin trial, an indi-
vidual destined to have a heart attack within the 5-year observation period must have had advanced atherosclerosis when entering the trial. Indeed, the degree of protection in statin trials increases with duration (3, 15).

The lesson of PCSK9 is clear. If we are to attain an 88% reduction in the incidence of coro-
nary heart disease, we must lower LDL levels well before atherosclerosis has become advanced. If we start early enough, it may be sufficient to lower LDL-C concentration only to 100 mg/dl, a goal that should be attainable for most people. These individuals must be prepared for lifetime treatment. Early intervention is designed to prevent a heart attack that might not occur for many years.

The physiological means to lower LDL concentration is through a stringent diet that is low in cholesterol and saturated fat. If this fails, drugs can be used. These include statins, cholesterol-absorption inhibitors, and bile acid–binding resins, all of which function by depleting the liver of cholesterol and increasing the number of hepatic LDL receptors. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-controlling enzyme in cholesterol synthesis (16). This action depletes liver cholesterol and activates a transcription factor called SREBP (sterol regulatory element–binding protein), which increases the expression of mRNA encoding LDL receptor (17). The increased numbers of LDL receptors produce a selective fall in LDL concentration (18). Statins have been in widespread use for 20 years, and placebo-controlled studies in 90,056 patients have shown a very
Dissolved Natural Organic Matter as a Microreactor

John P. Hassett

Almost all organic molecules dissolved in fresh and marine waters come from natural sources, ultimately derived from decay of algae and higher plants. These molecules form a very complex mixture whose underlying molecular structures are poorly characterized (1). Consequently, they are often referred to in aggregate as dissolved organic matter (DOM) and quantified as dissolved organic carbon (DOC). They are also referred to as aquatic humic substances, in recognition of a similarity between freshwater DOM and soil organic matter. Although chemical characterization of DOM is elusive, properties of DOM that influence the physical and chemical behavior of natural and pollutant ions and molecules in water have often been investigated. On page 1743 of this issue, Latch and McNeill (2) present a striking study of how DOM can enhance the reactivity of a hydrophobic molecule by bringing it into close association with a photochemically produced, short-lived reactant, singlet oxygen.

Hydrophobic contaminants in water are a major concern. Those that are chemically and biologically stable, such as the insecticide DDT, accumulate in aquatic food chains and can reach levels that threaten fish-eating organisms such as humans and predatory birds. Some, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), are very toxic. Others, such as natural and synthetic steroid hormones, can disrupt endocrine functions in aquatic organisms. DOM has both hydrophobic and hydrophilic properties. Therefore, it is able to bind other molecules by hydrophobic interactions. Hydrophobes in apparent solution in natural waters may thus exist in two states: one that is truly dissolved and one that is bound to DOM (see the figure). This binding decreases a hydrophobe’s apparent volatility, bioavailability, and attachment to particles and increases its apparent solubility. Binding also brings a hydrophobe into a chemical environment that is distinct from water, and so can affect its reactivity.

DOM contains groups (chromophores) that absorb sunlight. Absorbance is strongest in the ultraviolet but often extends into the visible portion of the spectrum, giving the brown color often associated with water from wetlands (bogs, peatlands, and swamps). Absorption of light by this chromophoric DOM (CDOM) can lead to formation of short-lived reactive products such as singlet oxygen ($^1O_2$). Although many of these products can react with hydrophobic compounds in water, their concentrations as measured with hydrophilic probes (furfuryl alcohol in the case of singlet oxygen) are too low to be important even at diffusion-controlled rates. However, Blough (3) and Burns et al. (4) have demonstrated that ions or molecules associated with DOM encounter higher concentrations of short-lived reac-

References and Notes
24. M.S.B. holds shares of stock in Merck and Pfizer, two companies that discovered and market cholesterol-lowering drugs. He is on the board of directors of Pfizer. J.L.G. holds shares in five companies that discovered and market cholesterol-lowering drugs (Astra Zeneca, Bristol-Myers Squibb, Merck, Pfizer, and Schering-Plough). Since 2003, he has received consulting fees from two companies that develop drugs and related strategies to lower cholesterol (Schering-Plough and Amgen). The authors do not have planned, pending, or awarded patents related to the work discussed here, nor do they have relationships with companies that market generic drugs. Authors receive research support from the NIH and the Perot Family Foundation.